PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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-2 JAN 2001

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PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	29.12.2000
Applicant's or agent's file reference: PWC/P21647WO	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/00908	13/03/2000	12/03/1999

International Patent Classification (IPC) or both national classification and IPC

G01N33/574

Applicant

OXFORD GLYCOSCIENCES (UK) LTD. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☒	Certain document cited
VII	☒	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 12/07/2001.

Name and mailing address of the international preliminary examining authority:

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Authorized officer / Examiner

Jacques, P

Formalities officer (incl. extension of time limits)

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I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".)*:

Description, pages:

1-76 as originally filed

Claims, No.:

1-23 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 12, 13-17 and 21-22(with respect to industrial applicability),

because:

   ☒ the said international application, or the said claims Nos. 21-22 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 13-17 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☒ the claims, or said claims Nos. 12 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:
see separate sheet

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrialapplicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-7, 9-11 (No)
Inventive step (IS)	Claims	8, 18-23 (No)
Industrial applicability (IA)	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Re Item I

Basis of the opinion

1. Sequence listing pages 1-44 filed with the letter of 24.05.2000 do not form part of the application (Rule 13ter.1(f) PCT).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 21-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).
   In this context, the said claims are considered to fall under the concept of methods of treatment.

2. The subject-matter of claim 12 is not convincingly supported by the description (Article 6 PCT) which would give sufficient guidance to a person skilled in the art to carry out the invention (Article 5 PCT). Thus, novelty, inventive step and industrial applicability cannot be assessed (see further point 4 under Item VIII).

3. The subject-matter of claims 13-17 is so unclear (Article 6 PCT) that novelty, inventive step and industrial applicability cannot be assessed (see further point 5 under Item VIII).

Re Item IV

Lack of unity of invention

1. The subject-matter of claim 1 does not meet the requirements of Rule 13 PCT for the following reasons:
   claim 1 relates to a method for screening for breast cancer which comprises the step of identifying the presence or absence of one or more of 51 different proteins. it

would appear that all the embodiments of the present invention share the common feature that the said proteins are involved in breast cancer thus being breast cancer markers.
However, documents D1 to D7 disclose various methods for identifying patients suffering from breast cancer based on the identification of markers including those disclosed in the present application (see further point 4 of section V).
Thus, as the said proteins are known breast cancer markers, the requirements of unity of invention is not fulfilled in that there is no technical relationship among the said markers as they do not involve one or more of the same corresponding special technical features.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: BINI LUCA; MAGI BARBARA ET AL.: 'Protein expression profiles in human breast ductal carcinoma and histologically normal tissue' ELECTROPHORESIS, vol. 18, December 1997 (1997-12), pages 2832-2841,

D2: FRANZEN BO; LINDER STIG ET AL.: 'Analysis of polypeptide expression in benign and malignant human breast lesions' ELECTROPHORESIS, vol. 18, 1997, pages 582-587,

D3: WILLIAMS KATHERINE; CHUBB CYNTHIA; HUBERMAN ELIEZER; GIOMETTI CAROL S: 'Analysis of differential protein expression in normal and neoplastic human breast epithelial cell lines' ELECTROPHORESIS, vol. 19, February 1998 (1998-02), pages 333-343,

D4: US-A-5 158 893 (HACKETT ADELINE J ET AL) 27 October 1992 (1992-10-27),

D5: US-A-4 775 620 (CARDIFF ROBERT D ET AL) 4 October 1988 (1988-10-04),

D6: US-A-5 798 266 (QUAY STEVEN C ET AL) 25 August 1998 (1998-08-25),

D7: US-A-5 188 964 (MCGUIRE WILLIAM L ET AL) 23 February 1993 (1993-02-23).

2. Document "WO 9617080" cited as an X-document in the International Search Report has not been considered as pertinent in the art as the said document discloses the cytokeratin 20 as breast cancer marker, however the said cytokeratin is not disclosed in the present application.

3. The documents cited as P-documents in the International Search Report are not to be regarded as state of the art according to Article 33(2) PCT, as the date of priority claimed can be allowed for the relevant parts of the present application.

4. Notwithstanding the objections raised under Article 6 PCT (see points 1, 2 and 3 under Item VIII), the subject-matter of claim 1 is not new (Article 33(2) PCT) for the following reasons:
document D1 discloses a two-dimensional electrophoresis (2-DE) analysis method allowing to attribute the significance of tumor markers to a definite pattern consisting of 32 electrophoretic spots whose intensity was enhanced in ductal carcinoma over histologically normal tissue (see page 2832, right column, lines 20-24). Moreover, spots assigned to markers include those used in the present application, e.g. fructose biphosphate aldolase, thioredoxin.
Similarly, document D2 discloses a (2-DE) method for screening of proteins expressed in breast cancer in a biological sample obtained from a human subject. The said document discloses that cytokeratins and tropomyosins (as disclosed in the present application) are lower in carcinomas compared to fibroademonas (see abstract).
Document D3 also discloses a 2-DE method suitable for identifying breast cancer, wherein the expression of hsp27 was found to be increased in breast carcinomas (abstract and page 341, right column to page 342, left column, first paragraph).
Document D4 discloses a method for identification and diagnosis of human mammary and other carcinoma, the said method being based on the identification of the 51000 Dalton keratin 14 (as disclosed in the present application) (see column 2, line 50 to column 3, line 2).
Documents D5, D6 and D7 disclose various method for identifying patients suffering from breast cancer based on the identification of markers including those disclosed in the present application, like cytokeratins 8 and 18 (see D5 abstract and claim 3), cathepsin D (see D6, abstract) or hsp27 and hsp90 (see D7, abstract).

Thus all the features of claim 1 are already known from the above cited documents.

The IPEA has however noted that the said known breast cancer markers as defined in tables I to IV, identified by 2-DE analysis, are differentially expressed in breast luminal epithelial cells over myoepithelial cells, thus making the said markers specific of the said cell type. Among the disclosed markers, it would however appear that the breast cancer markers cytokeratins 8 and 18 are known to be luminal specific (D3, page 342, second paragraph). It appears that all other known breast cancer markers have not been disclosed in the cited prior art as being "luminal specific".

5. The same reasoning as for claim 1 applies to independent claims 2 and 3 as the methods disclosed in the prior art (see above point 4) appear to be suitable for monitoring and/or assessing breast cancer treatment (claim 2) or identifying the presence or absence of metastatic breast cancer cells (claim 3).
Thus the subject-matter of the said claims is not new (Article 33(2) PCT).

6. The same applies to dependent claims 4-7 for the following reasons:
the biological sample in D1 is a tissue sample (Materials and methods section)(claim 4), D1 discloses the identification of a cluster of markers, among them thioredoxin and fructose biphosphate aldolase (abstract) (claim 5), document D3 discloses a non-competitive immunoassays utilising antibodies against cytokeratin 19 and hsp27 (page 337, "protein identification" paragraph) (claims 6-7).

7. Notwithstanding the objection raised under Article 6 PCT (see point 3 under Item VIII), as the particular combination of features of dependent claim 8 is not disclosed in any cited prior art, the subject-matter of the said claim would appear to be novel (Article 33(2) PCT).

However, the subject-matter of the said claim does not involve an inventive step in the sense of Article 33(3) PCT as it falls within the normal design capabilities of the skilled man to use nucleic acid probes to amplify known nucleic acids of known markers.

8. As the particular combination of features of dependent claim 18 is not disclosed in any cited prior art, the subject-matter of the said claim would appear to be novel

(Article 33(2) PCT).

However, the subject-matter of the said claim does not involve an inventive step in the sense of Article 33(3) PCT as the skilled man would be able to apply the known method of claim 1 to scan a whole body or organ.

Dependent claims 18-19 do not appear to contain any additional features which meet the requirements of inventive steps as all the features of these claims are conventional in the art.

9. Notwithstanding the objection raised under Article 6 PCT (see point 2 under Item VIII), the subject-matter of claim 9 is not new (Article 33(2) PCT) for the following reasons:
document D3 discloses anti-cytokeratin 19, anti-hsp70 and anti-hsp90 monoclonal antibodies (page 337, "protein identification" paragraph). D4 discloses a monoclonal antibody specifically reactive with keratin 14 (claim 6). D5 discloses antibodies against cytokeratins 8 and 18 (column 4, lines 57-68). D7 discloses monoclonal antibody against hsp70 (column 18, lines 14-15).
Thus all the features of claim 9 are already known from the above cited documents.

The same applies to dependent claims 10 and 11.

10. Notwithstanding the objection raised under Article 6 PCT (see point 2 under Item VIII), as the particular combination of features of independent claim 21 is not disclosed in any cited prior art, the subject-matter of the said claim would appear to be novel (Article 33(2) PCT).

However, the subject-matter of the said claim does not involve an inventive step in the sense of Article 33(3) PCT as it falls within the normal design capabilities of the skilled man to administer to a subject suffering from breast cancer, known antibodies against known proteins involved in the said breast cancer, the said antibodies being conjugated to known agent capable of causing cell death.

11. The same applies to dependent claim 22 which does not contain any additional features which meet the requirements of inventive steps as they are conventional in

the art (Article 33(3)PCT).

12. Notwithstanding the objection raised under Article 6 PCT (see point 2 under Item VIII), as the particular combination of features of independent claim 23 is not disclosed in any cited prior art, the subject-matter of the said claim would appear to be novel (Article 33(2) PCT).

However, the subject-matter of the said claim does not involve an inventive step in the sense of Article 33(3) PCT as it falls within the normal capabilities of the skilled man to manufacture a medicament for treating cancer with known antibodies against known proteins involved in breast cancer.

13. For the assessment of the present claims 21-22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 to D7 is not mentioned in the description, nor are these documents identified therein.

✓ 08/980,574 = US 6064754

2. References to U.S. application serial numbers (page 6, line 10) should be replaced by the corresponding publication numbers, provided the publication date was prior to the effective date of the present application. Otherwise, a family member application, pre-published, should be cited. If not, the reference should be deleted (see further PCT Guidelines, C II, 4.18).

3. Claims 18-20, which are dependent to claim 1 to 5, should be grouped together with

the claims on which they are dependent (Rule 6.4(c)).

Re Item VIII

Certain observations on the international application

1. It is clear from the whole description, and more particulrly from page 8, lines 21-27 and page 12, lines 26-31 that the following feature is essential to the definition of the invention:

   (1) a biological sample obtained from breast luminal epithelial cells from said human subject

   Since independent claims 1, 2 and 3 do not contain this feature it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

2. The term "protein features" (claims 1-3, 9, 14, 21 and 23) is vague and unclear (Article 6 PCT), thus the matter for which protection is sought is not clearly defined.

3. Claims 1, 2 and 3 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claims attempt to define the subjet-matter in terms of result to be achieved, which is identifying the presence or absence of one or more of the protein features. However, such a formulation is not allowable because it seems possible to define the subject-matter in more concrete terms, for instance in terms of how the identification of the protein feature is achieved.

   Furthermore, it would appear that the above mentioned "protein features" refer to spots in a 2D gel, the said spots being characterized by their molecular weight and pI (see tables I and II). Moreover, it would appear that identifying only the presence or the absence of one or more of the said markers would not allow to diagnose breast cancer as the said markers are also expressed, in different levels, in cancer-free tissue.
   Therefore, it would appear that the methods of claims 1, 2 and 3 are based on the

comparisons of the protein expression maps (comparisons of the proteomes) of breast luminal epithelial cells of a human subject with the same tissue of a subject free of cancer.

However, if this is the case, it appears unclear how the method of claim 8 can be performed with regard to the protein features as defined in tables I and II.

Such inconsistencies renders the scope of claims 1, 2, 3 and 8 unclear and therefore the matter for which protection is sought is not at all clear (Article 6 PCT).

4. Claim 12 does not meet the requirements of both Articles 5 and 6 PCT for the following reasons:

The claim defines the subject-matter in terms of result to be achieved, which is adapting/modifying the antibody in a manner such that binding to the protein will be localised to the site of the breast cancer cells. However, from the description it is not at all clear how the said effect is to be achieved, the particular modification/adaptation of the antibody is not disclose.

The subject-matter of the claim is thus not convincingly supported by the description (Article 6 PCT) which would give sufficient guidance to a person skilled in the art to carry out the invention (Article 5 PCT).

5. The subject-matter of claim 13, relating to a kit, does not define the nature of the reagents of the said kit and thus the subject-matter for which protection is sought is not defined.

Claim 13 is therefore so unclear (Article 6 PCT) that novelty, inventive step and industrial applicability can not be assessed.

The same applies to claims 14-17 which only partially define the content of the kit.